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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/077,435	02/15/2002	M. Vijay Kumar	M0351-268908	3474

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Cynthia B. Rothschild
Kilpatrick Stockton LLP
1001 West Fourth Street
Winston-Salem, NC 27101

EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/077,435	KUMAR, M. VIJAY	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 March 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-12,18-22,25,26,28-38,42,43 and 47-52* is/are pending in the application.

4a) Of the above claim(s) *2-12, 18-22, 25, 26,* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-38,42,43 and 47-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant cancels claims 45-46.

Accordingly, claims 28-38, 42-43, 47-52 are being examined.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claims 28-38, 47-52 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Bonavida, B et al, 1999 (Intl J Oncology, 15(4): 793-802, of record), in view of Wiley et al (WO 97/01633-A1), El Etreby et al, 2000 (The Prostate 42: 99-106, IDS # 27, submitted on 11/12/02, of record), and El ETreby et al, 1998 (Breast Cancer Res Treat, 51: 149-168), for reasons already of record in paper of 10/13/06.

A. The response asserts that there is no motivation to combine the references with a reasonable expectation of success, such that all the limitations in the claims are taught or suggested. The response asserts that there is no description in Bonavida et al that actinomycin D, a non-specific inhibitor of transcription of all mRNAs, overcome resistance to TRAIL via inhibition of Bcl-XL, or Bcl-2, or other anti-apoptotic proteins. The response asserts that with

respect to prostate cancer, Bonavida et al teach that there is no correlation between expression of prostate cancer cell death receptors (DR4, DR5, DcR1 and DcR2) and the sensitivity of the cells to killing by TRAIL and actinomycin D, indicative that the action of actinomycin D is not via pathway involved DR4 and/or DR5. The response concludes that thus one would **not be motivated** to use TRAIL for the treatment of prostate cancer, as the effect for TRAIL and actinomycin does not appear to be specific for the death receptors known to mediate the effects of TRAIL. The response concludes that also, reading Bonavida et al, one would have a very **low expectation of success** of using another agent in combination with TRAIL, by increasing apoptosis in a specific, death receptor-mediated manner. The response asserts that Bonavida et al only suggests that certain relatively nonspecific agents may be combined with TRAIL to increase cell killing. The response asserts that on the contrary Gliniak et al, previously recited by the Examiner, teach that many chemotherapeutic drugs which are expected to reduce apoptosis do not result in enhancemenat of cytotoxic activity by TRAIL.

The response has been considered but is not found to be persuasive for the following reasons:

The response argues individual reference, rather than a combination of references.

It is noted that the instant claims are composition claims, and are not method claims.

Contrary to the response's argument, Bonavida et al teach a **specific** agent to combine with TRAIL to overcome resistance to TRAIL-mediated apoptosis. Said agent is the inhibitor of the anti-apoptotic protein, Bcl-XL or Bcl-2, similar to Actinomycin D, which inhibits Bcl-XL (p.800, first column, item 7, Mechanism of TRAIL-resistance and sensitization). Further, although Actinomycin D also kills cells by termination of mRNA transcription, cell death by

termination of mRNA transcription is **not** the same as apoptosis, and could be distinguished from apoptosis, because apoptosis involves activation of caspases and cell death by DNA fragmentation (see for example Figure 1 on page 796 of Bonavida et al). The percentage of **apoptotic cells** clearly is increased by treating with Actinomycin D in combination with TRAIL, as shown in table III, on page 799 in Bonavida et al, indicating that Actinomycin D acts to sensitise TRAIL resistance via the apoptotic pathway, i.e. inhibiting the anti-apoptic protein Bcl-XL, resulting in increasing apoptotic cells, as concluded by Bonavida et al (p.800, first column, item 7, Mechanism of TRAIL-resistance and sensitization).

Further, Bonavida et al **do not teach** that there is no **correlation** between expression of prostate cancer cell death receptors (DR4, DR5, DcR1 and DcR2) and the sensitivity of the cells to killing by TRAIL **and** actinomycin D. The reference is **silent** concerning the effect of actinomycin D on the expression pattern of DR4 and/or DR5. In table IV on page 799, in Bonavida et al, only TRAIL-mediated apoptosis, and **not** actinomycin D cell killing, is recited. That is, from table IV, only prostate cancer cells, that are "resistant to TRAIL killing", do not show a consistent level of DR4 or DR5 receptors, and their patterns of expression do not correlate with their being resistant to TRAIL killing (p.799, first column, paragraph before last).

Thus, Bonavida et al provide **motivation** for the use TRAIL and a compound that suppresses an anti-apoptotic molecule, such as Bcl-XL or Bcl-2, because compounds such as actinomycin D, that decreases the expression of Bcl-XL, together with TRAIL, overcome the resistance to TRAIL-mediated apoptosis, as taught by Bonavida et al.

Moreover, the composition taught by the combined art would be useful for successful treating of both androgen-responsive and non-responsive prostate cancers, because Mifepristone

inhibits growth of both androgen-responsive and non-responsive prostate cancers, as taught by El-Etreby et al, 2000, in addition to restoring the apoptotic action of TRAIL.

Concerning Gliniak et al, it is noted that Gliniak et al is not recited in the present 103 rejection to simplify the issue. The teaching of Gliniak et al reinforces the strategies taught by Bonavida. Although Gliniak teaches that combining TRAIL with many chemotherapeutic agents, including cisplatin, 5-FU, mitomycin, etopside or adriamycin did not result in enhancement of cytotoxicity, Gliniak teaches mechanism of action of compounds that do synergize with TRAIL. That is Gliniak et al teach that in a manner similar to actinomycin D, and cyclohexamide, campthothecin, an inhibitor of topoisomerase I, synergizes with TRAIL, by ultimately inhibiting the synthesis of an apoptosis-regulatory protein (p.6158, first column). Thus from the teaching of Gliniak et al, one would choose among various chemotherapeutic agents those that inhibit the synthesis of an apoptosis-regulatory protein to enhance cytotoxicity.

B. The response asserts that EL-Etreby, 2000, does not describe or suggest the use of TRAIL for inhibition of prostate cancer, and does not describe, teach, or suggest that Mifepristone, or other antiprogestins, may be used to increase the sensitivity of TRAIL-resistant, androgen-sensitive prostate cancer cells, such as LNCaP cells, or that compositions having this ability may be clinically important. The response asserts that nor, does E1 Etreby 2000, in combination with Bonavida or E1 Etreby 1998 (discussed below), describe, teach or suggest that antiprogestins, such as Mifepristone, may act in a synergistic manner with TRAIL, at the level of the TRAIL pathway.

The response asserts that El-Etreby et al, 1998, teach that Mifepristone can inhibit breast cancer growth and the synthesis of bcl-2. The response asserts that although bcl-2 is known to be expressed in androgen-insensitive prostate cancer cells (e.g., LNCaP C4-2), it is not detected in significant amounts in androgen-sensitive cells, such as the TRAIL-resistant LNCaP cells described by the Applicant (see e.g., Chaudhary et al., Environ. Health Perspectives, 1999, 107(Suppl- 1):49-57 at page 53, col. 2; submitted herewith as a Supplemental IDS). The response asserts that in contrast, Applicant has shown that it is the androgen-sensitive prostate cancer cells that are refractory to treatment with TRAIL. The response concludes that thus, one reading E1-Etreby 1998 would not be motivated to use Mifespristone to increase bcl-2 in prostate cancer as a means to overcome resistance to TRAIL via inhibition of bcl-2 or other members of the apoptotic pathway, as there was no evidence that the activity of bcl-2 is significant in the type of prostate cancer cells that are resistant to TRAIL, i.e. androgen-sensitive LNCaP cells. The response asserts that thus El-Etreby et al,1998, teach away from the claimed invention, because it would not be expected that Mifepristone induces apoptosis by inhibition of bcl-2 in androgen-sensitive cells.

The response asserts that the art does not teach or suggest a synergy between TRAIL and an antiprogestin, or activating the DR4/DR5 receptor pathway.

The response concludes that thus, the combination of the references, Bonavida, El Etreby 2000 and E1 Etreby 1998, in view of the sequence provided by Wiley, to not describe, teach or suggest the limitations of a composition (or method) for treating prostate cancer by inducing cell death in androgen responsive and androgen independent prostate cancer cells comprising an effective amount of the TRAIL protein SEQ ID NO: 1 and an antiprogestin in a pharmaceutical

carrier, wherein said effective amount induces apoptosis and to increase at least one of the DR4 or the DR5 death receptors in at least a portion of the treated prostate cancer cells exposed to the composition such that the combination of the TRAIL and the antiprogestin induces apoptosis in a greater number of the treated androgen responsive and androgen independent prostate cancer cells than the additive effect of TRAIL and the antiprogestin separately applied to the cancer cells.

The response has been considered but is not found to be persuasive for the following reasons:

Contrary to the response's assertion, El-Etriby et al, 2000, and 1998 provide motivation for combining with Bonavida et al. One would have been **motivated** to substitute actinomycin D taught by Bonavida et al with Mifepristone taught by El-Etreby et al, 2000, 1998, because Mifepristone inhibits the anti-apoptotic protein Bcl-2, as taught by El-Etreby et al, 1998, and acts similarly to actinomycin D, which inhibits the anti-apoptotic protein Bcl-XL, both of which anti-apoptotic proteins are suggested by Bonavida as targets of drugs that sensitize TRAIL-mediated apoptosis.

Further, whether androgen-sensitive prostate cancer cells have low level of Bcl-2 is not germane to the motivation for combining Mifepristone with TRAIL, because: 1) other cancers that are resistant to TRAIL, such as the androgen-insensitive prostate cancer DU145, or Kaposi's sarcoma, as taught by Bonavida et al, have increased expression of anti-apoptotic proteins, such as Bcl-2, or Bcl-XL, respectively, as confirmed in Chaudhary et al (p.53, second column, first paragraph) or taught by Bonavida et al, respectively, and 2) two strategies can be used to sensitize resistant cancer cells to TRAIL-mediated apoptosis, one is the **suppression of** anti-

apoptotic molecule, another is the up-regulation of pro-apoptotic molecule; for example **Bcl-XL and BCL-2**, major inhibitors of the mitochondrial apoptotic pathway, as taught by Bonavida et al (Bonavida et al, p.800, first column, item 7, Mechanism of TRAIL-resistance and sensitization)..

Moreover, the composition taught by the combined art would be useful for successful treating of both androgen-responsive and non-responsive prostate cancers, because Mifepristone inhibits growth of both androgen-responsive and non-responsive prostate cancers, as taught by El-Etreby et al, in addition to restoring the apoptotic action of TRAIL.

Further, although the references do not explicitly teach that the composition comprising TRAIL and the antiprogestin Mifepristone induces apoptosis and increases at least one of the DR4 or the DR5 death receptors in at least a portion of the treated androgen-responsive and androgen-independent prostate cancer cells, and that said composition induces apoptosis in a greater number of the treated androgen responsive and androgen independent prostate cancer cells than the additive effect of TRAIL and the antiprogestin separately, however, the claimed composition appears to be the same as the prior art composition, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

2. Claims 42-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bonavida, B et al, 1999 (Intl J Oncology, 15(4): 793-802), in view of Wiley et al (WO 97/01633-A1), El Etreby et al, 2000 (The Prostate 42: 99-106, IDS # 27, submitted on 11/12/02), and El Etreby et al, 1998 (Breast Cancer Res Treat, 51: 149-168), and further in view of Presta et al (20020146416, having as priority, March 18, 1994), for reasons already of record of paper of 10/13/06.

The response asserts that Claims 42-43 are not obvious over Bonavida, Wiley, El-Etreby 2000, and 1998, for reasons stated above, and that Presta does not overcome the deficiencies of these references.

Claims 42-43 are obvious over Bonavida, Wiley, El-Etreby 2000, and 1998, for reasons stated above.

It would have been obvious to package TRAIL polypeptide and Mifepristone taught by Bonavida et al, WO 97/01633-A1, El Etreby et al, 2000, and El Etreby et al, 1998, in a kit and packaged in a sterile container, with instruction for use, for commercial application.

Moreover, it would have been obvious to formulate the TRAIL polypeptide and Mifepristone composition taught by Bonavida et al, WO 97/01633-A1, El Etreby et al, 2000, and El Etreby et al, 1998, in a pharmaceutical carrier, as taught by Presta et al, for storage of the polypeptides.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, SHANON FOLEY can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MINH TAM DAVIS
April 19, 2007

SHANON FOLEY
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600